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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,061	10/06/2000	Stephen H. Bartelmez	0450-0031.30	2847

7590 04/12/2004

Iota Pi Law Group
P O Box 60850
Palo Alto, CA 94306-0850

EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/12/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No. 09/684,061	Applicant(s) BARTELMEZ ET AL.	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5,6,10,19,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19 and 22* is/are allowed.

6)☒ Claim(s) *3,5,6,10 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 1-7-04.

Claims 3, 5, 6, 10, 19, 21 and 22 are pending in the instant application.

The allowability of claim 6 has been withdrawn in light of the new rejections set forth below.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections and Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5, 6, 10 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear in claim 6, lines 3-4, what is meant by one or more antisense with the sequence presented as SEQ ID NO: 1 (e.g. Does "one or more" refer to antisense oligonucleotides, all comprising SEQ ID NO: 1, but differing with respect to their intersubunit linkages? Or does this refer to antisense oligonucleotides comprising

different nucleotide subsequences from SEQ ID NO: 1?) Appropriate clarification is requested.

It is also unclear in claim 3, lines 1- 2, with respect to claim 6, line 4, how one or more antisense oligomers have a length of about 12 to 25 bases, yet have the sequence presented as SEQ ID NO: 1. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 5, 6, 10 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro decrease in the number of high proliferative potential colony forming cells (HPP-CFCs) (i.e. cells that proliferate in response to rat rSCF, mouse rIL-3 and human rIL-6) relative to the number of clonogenic cells following exposure of the cells to antisense of SEQ ID NO: 1, does not reasonably provide enablement for a method of promoting hematopoietic stem cell differentiation (e.g. into an array of distinctly defined, differentiated populations of progenitor cells) comprising the administration of SEQ ID NO: 1 in vitro, nor for infusing the antisense treated population back into a subject, whereby target gene inhibition is maintained and differentiation into various progenitor cells is obtained in the reinfused, antisense treated cells The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of promoting hematopoietic stem cell differentiation comprising contacting hematopoietic stem cells in vitro with an antisense of SEQ ID NO: 1, and infusing the antisense treated cells back into a subject.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of stem cell directed gene therapy (including antisense therapy) using hematopoietic stem cells. Srour et al discuss the potential advantages of ex vivo expansion of hematopoietic stem and progenitor cells in somatic gene therapy (Srour et al. J. Hematotherapy 8: 93-102, 1999). Hurdles to overcome in achieving successful therapy using stem cells include a repeated failure to sustain induced cell division and proliferation of stem cells while at the same time being able to maintain primary functional characteristics of stem cells, including sustaining long term hematopoiesis. ."...studies demonstrate that over a reasonable time period, the numbers of assayable progenitor cells increase several fold in culture, then rapidly decline. Whether this decline results from adverse effects of in vitro expansion or is due to natural senescence of more mature HPC is difficult to assess." (page 94, right hand column of Srour et al). According to Srour, three major areas of concern regarding hematotherapy include the ability to achieve cell cycle activation and progression, the ability to achieve changes in homing and adhesion properties of stem and progenitor cells, and the ability to rapid differentiation and

lineage commitment under the influence of or in response to an imbalance in positive and negative regulation in vitro (page 95, top left hand column).

Engel and Kohn, in an article addressing the feasibility of stem cell directed gene therapy in treating HIV, discuss some shortcomings that are currently being addressed in the field: "Clinical trials performed to date in which hematopoietic cells ... have been transduced with retroviral vectors and then reinfused have produced low to undetectable levels of gene containing peripheral blood leukocytes. New vector ... systems... need to be developed to ensure efficient gene transfer and persistent transgene expression to provide lifelong resistance to the cells targeted..." (Engel et al. Frontiers in Bioscience 4, e26-23, 1999, page 26, left hand column). According to Engel, relatively low gene transfer and subsequent gene expression in differentiated pluripotent human HSC is often unsatisfactory. Similar frustrations of low frequency of antisense (ribozyme) containing cells following cell reinfusions into patients are also routinely encountered (See e.g. Engel bottom page 28-top page 29).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of promoting hematopoietic stem cell differentiation into various and defined pluripotent cells in vitro or ex vivo upon antisense administration. The specification teaches the administration in vitro of SEQ ID NO: 1 to isolated murine hematopoietic stem cells whereby an alteration of phenotype is observed in the target cells, which phenotype is a decrease in the number of HPP-CFC cells relative to clonogenic cells. This observation is not commensurate with the ability

to promote hematopoietic stem cell differentiation into any mature cell comprising administration of antisense in vitro. Nor is it commensurate with achieving sustained stem cell differentiation upon infusion of antisense treated stem cells back into a subject. One skilled in the art would not accept on its face the examples given in the specification of in vitro transfection into hematopoietic stem cell isolates of SEQ ID NO: 1, which targets the mRNA encoding Evi-1 zinc finger protein, as being correlative or representative of the successful inhibition of cellular proliferation or increasing the number of lineage committed progenitor cells and their progeny in vivo upon infusion of antisense treated stem cells in view of the lack of guidance in the specification and known unpredictability associated with sustained antisense inhibition of a target gene in stem cells which have been reinfused into a subject and further whereby the various forms of HPC differentiation have been achieved. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vitro stem cell differentiation upon antisense administration or upon reinfusion of antisense treated stem cells into a subject

The breadth of the claims and the quantity of experimentation required. The claims are drawn to a method of promoting hematopoietic stem cell differentiation comprising contacting hematopoietic stem cells in vitro with an antisense of SEQ ID NO: 1, and infusing the antisense treated cells back into a subject. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of various forms of stem cell differentiation in vitro, and upon reinfusion into a subject, following administration of SEQ ID NO: 1 in vitro. Since the specification

fails to provide any particular guidance for determining differentiation of HPC into various progenitor cells upon administration of antisense, and further upon reinfusion into a subject, and since determination of these factors for a particular form of differentiation or development of a particular progenitor cell upon antisense administration is highly unpredictable in vitro and upon reinfusion into a subject, it would require undue experimentation to practice the invention over the scope claimed.

Allowable Subject Matter

Claims 19 and 22 appear to be free of the prior art of record.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ

3-30-04